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Improving Resectability of Hepatic Colorectal Metastases: Expert Consensus Statement

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DOWNSTAGING OF UNRESECTABLE METASTASES AND TIMING OF LIVER RESECTION

Colorectal cancer is the third most common malignancy in Western countries.[1,2] Approximately 50% of patients with colorectal cancer develop hepatic metastases during the course of the disease.[3–5] The liver is the most common site of metastases of colorectal cancer, and hepatic metastases are responsible for death in at least two thirds of patients with colorectal malignancy.[3,4]

At present, the only accepted potentially curative standard treatment in patients with liver metastases of colorectal cancer is liver resection. After resection, the 5-year overall survival rate in selected patients is 37%–58% in recent series.[6–11] Although only 10%–20% of patients with hepatic colorectal metastases are eligible for resection, the absolute number of patients amenable to resection is large and is growing with better imaging, better surgery, and improvements in systemic therapies to reduce the risk of both intrahepatic and extrahepatic recurrences.[3,12–16] For patients with liver metastases, a multidisciplinary team approach has become mandatory.

Advances made by chemotherapy have been the major determinant of new therapeutic approaches concerning primarily unresectable patients. Until recently, patients with unresectable hepatic colorectal metastases were treated with palliative chemotherapy, and almost no such patients survived for 5 years.[17,18] Recently, advances in chemotherapy have permitted resection in some patients with initially unresectable metastases.

Chemotherapy regimens based on 5-fluorouracil (5-FU) rarely provided sufficient intrahepatic tumoricidal effect to convert hepatic metastases from unresectable to resectable (response rate < 20%). However, novel chemotherapeutic regimens combining 5-FU, folinic acid, and oxaliplatin and/or irinotecan[19–26] have been associated with improved response rates (around 50%), allowing 10%–30% of patients with initially unresectable hepatic metastases to be rescued by liver surgery.[13,14,22] In addition, early results from trials evaluating several novel biologic agents, including cetuximab[27] and bevacizumab,[26] suggest that even more patients with initially unresectable disease may respond to primary

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treatment with combinations of systemic chemotherapy, with response rates of 70% or more.[28,29]

Long-term Outcomes Following Hepatic Resection in Patients Converted to Resectable Status by Systemic Chemotherapy

Although numerous studies have been published describing response and resection rates following systemic and/or regional chemotherapy for patients with initially unresectable hepatic colorectal metastases,[30] only four of these studies have included long-term outcomes analyses.

The first of these studies[13] is a retrospective update of a single-institution experience first reported in 1996.[31] At the time of the 2004 update, the study cohort included 1,104 patients with anatomically unresectable disease. Following a mean of ten cycles of systemic chemotherapy (mainly chronomodulated oxaliplatin + 5-FU-based regimens), 12.5% of patients were converted to resectable status. In 93% of these cases, a curative hepatectomy was performed. Following hepatic resection, 5-year and 10-year overall survival rates were 33% and 23%, respectively, and disease-free survival rates were 22% and 17%, respectively. Poor prognostic factors included primary lesion in the rectum, ≥ three metastases, size of the largest metastasis > 10 cm, and CA 19-9 level > 100 IU/l.

The second series is a phase II trial published by Zelek et al.[32] in 2003. This report included 31 patients with anatomically unresectable liver metastases treated with a combination of intravenous irinotecan, 5-FU, and folinic acid and hepatic arterial infusion of pirarubicin. This was a fairly toxic regimen (78% of patients had grades 3 or 4 of hematologic toxicity) that produced objective partial responses following a median of five cycles of treatment in 48% of patients based on World Health Organization (WHO) response criteria. Eleven patients (35%) subsequently underwent resection, and in nine (29%) of these cases, resection margins were negative. For the subset of patients with complete resections, median disease-free survival was 20.2 months and median overall survival had not been reached at the time of the report. Two- and 3-year overall survival rates for completely resected patients were 100% and 65%, respectively. The limited follow-up duration and a lack of events prevented analysis of prognostic factors that may have been associated with poor outcomes following hepatic resection.

The third study to report on outcomes after hepatic resection in patients with disease rendered resectable by chemotherapy is another phase II study, from Pozzo et al., published in 2004.[22] This group treated 40 patients deemed unresectable according to strict institutional policy criteria with a regimen containing irinotecan, folinic acid, and 5-FU. The mean number of cycles delivered was 15. By WHO response criteria, 48% of patients had an objective response. Sixteen patients (40%) underwent laparoscopic exploration, and 13 (33%) had their disease resected with negative margins. Median disease-free survival for patients who underwent surgery was 14.3 months, and all patients who underwent resection were alive at a median follow-up interval of 19 (range: 6–30) months. Prognostic factors were not investigated.

The final, and most recent, study to report outcomes data for patients with unresectable disease converted to resectable status by systemic therapy is from Alberts et al.[33] Their data were first reported in abstract form in 2001 and were updated in a formal report in October 2005. The patient cohort included 42 evaluable patients enrolled in a phase II trial of the North Central Cancer Treatment Group who were treated for unresectable colorectal liver metastases with the oxaliplatin-folinicacid-fluorouracil (FOLFOX4) regimen. Sixty percent of patients experienced a radiographic response, and 43% ultimately underwent hepatic resection. Fifteen patients had a complete resection, yielding a potentially curative resection rate of 37%. Unfortunately, within 2 years of hepatic resection, 11 (73%) of these 15 patients experienced a relapse, including more than 70% with recurrence in the liver. The reported median overall survival for patients who underwent hepatic resection was 26 months.

In addition to the prognostic factors mentioned above, another factor appears to influence long-term outcome after hepatic resection in patients treated with preoperative chemotherapy: the ability of chemotherapy to control the tumor just before liver surgery. In a recent study performed in 131 patients with more than three liver metastases,[14] Adam et al. demonstrated that tumor progression was an important adverse factor with respect to outcome following hepatic resection: 5-year survival rates were 8% in patients with progression during chemotherapy compared with > 30% in patients with stable disease or objective tumor response to chemotherapy. Therefore, tumor progression during preoperative chemotherapy should be considered a relative contraindication to resection.

Timing of Surgery after Chemotherapy and Techniques to Improve Resectability

In general, hepatic resection should be performed as soon as colorectal metastases become resectable.

The reasons are twofold: First, preoperative chemotherapy results in damage to the liver that may increase morbidity and mortality after hepatic resection.[34,35] Second, occasionally, preoperative chemotherapy results in a radiographic complete response (histologically confirmed in 7% or less) that jeopardizes the performance of an adequate liver resection.[13]

Advances in the surgical approach to patients with extensive liver involvement by primary tumor include: (1) preoperative portal vein embolization (PVE),[36] (2) liver resection combined with radiofrequency ablation (RFA) or cryosurgery,[37] and (3) two-stage hepatectomy.[38] By reducing the incidence of postoperative liver failure, optimizing the size of the future liver remnant (FLR) (preoperative PVE and two-stage hepatectomy), and permitting complete treatment of otherwise unresectable tumors (resection combined with RFA), these methods have increased the total number of patients who are candidates for hepatic resection.

Treatment of initially unresectable hepatic colorectal metastases has been characterized by remarkable advances over the past 15 years. Patients who years ago would only have been eligible for palliative chemotherapy now can take advantage of a variety of strategies available to render their disease surgically resectable, and in such patients who are ultimately able to undergo hepatic resection, long-term survival rates are 30%–35% at 5 years. These advances are the result of a strong collaboration between medical oncologists and surgeons. Development of new chemotherapy protocols has played a major role, offering the possibility of curative surgery to an increasingly large number of patients.

Consensus Statement

1. For patients with metastatic colorectal carcinoma isolated to the liver, hepatic resection is the only treatment associated with demonstrated long-term survival. All patients with resectable disease should be offered hepatic resection.
2. For patients with disease isolated to the liver that is deemed initially anatomically unresectable, preoperative chemotherapy permits complete resection in 15%–30% of patients.
3. In patients with initially unresectable hepatic colorectal metastases who undergo resection, the survival rate at 5 years (30%–35%) approaches the survival rate of patients who undergo upfront hepatic resection for initially resectable disease.
4. Preoperative chemotherapy results in damage to the liver that may increase morbidity and mortality after hepatic resection. Occasionally, preoperative chemotherapy results in a radiographic complete response (rarely histologically confirmed) that jeopardizes the performance of an adequate liver resection. For these reasons, the duration of neoadjuvant chemotherapy should be carefully considered, and resection should be performed as soon as hepatic metastases become technically resectable.
5. Radiological complete response is rarely associated with complete pathological response. Mapping and timing of resection are critical. Resection should encompass segments involved based on pre-chemotherapy imaging.

PVE AND EVALUATION OF THE FUTURE LIVER REMNANT (FLR)

PVE is a minimally invasive preoperative procedure advocated as a means for reducing risk for postoperative complications by increasing the mass of anticipated FLR. The rationale for PVE is that the increase in volume of the FLR, as a result of PVE, appears to improve liver function, as indicated by increased biliary excretion,[39,40] increased technetium-99m-galactosyl human serum albumin uptake,[41] and improvement in postoperative liver function tests following extended hepatectomy in patients undergoing PVE compared with no PVE.[42] The goal of PVE is to redistribute portal flow toward the segments of liver that will remain after surgery. PVE usually is performed percutaneously under sonographic and fluoroscopic guidance with the patient under conscious sedation in the interventional radiology suite.

Measurement of the FLR

The aim of "measurement" of the FLR is therefore not simply to assess the actual volume of the FLR but rather to predict the function of the FLR after removal of the tumor-bearing liver. Several methods for liver volume determination have been proposed. Most utilize computed tomography (CT) combined with three-dimensional (3D) CT volumetry.[42,43] With these methods, FLR volumes can be calculated accurately and reproducibly with errors of less than ± 5%.[44,45]

The FLR is generally standardized to total liver volume (TLV) and expressed in terms of percentage

of TLV that will remain after resection. It is possible to directly measure TLV using CT. However, direct measurement of TLV may not be relevant to surgical planning for two reasons. First, in patients with large tumors and in patients with liver disease, TLV is altered. Second, subtraction of tumor volume(s) from TLV results in additive mathematical errors in volume calculation.[46]

An alternative, accurate, and reproducible approach is to estimate TLV using a formula that relies on the linear correlation between TLV and body weight or body surface area.[42,47,48] A recent meta-analysis that compared 12 TLV formulas[49] revealed that the least biased and most precise formula for predicting TLV is $-794.41 + 1{,}267.28 \times$ body surface area.[47] Using the standardized FLR measurement in which FLR volume equals CT-measured FLR volume Υ calculated TLV, a correlation between the standardized FLR volume and postoperative outcome has been established.[42,50,51]

Indications and Contraindications for PVE

Indications for PVE depend on factors that impact the FLR volume needed for adequate post-hepatectomy liver function in an individual patient. Presence or absence of underlying liver disease, patient size (large patients require larger liver remnants than do smaller patients), and the extent and complexity of the planned resection must be considered in the setting of the patient's comorbidities, such as diabetes, that may affect hepatic regeneration. The volumetry technique detailed above integrates assessment of the actual FLR volume with patient size so that the standardized FLR volume can be used to determine the need for PVE based on the presence and extent of liver disease.

The FLR volume limit for safe resection varies from patient to patient. Guidelines have evolved from analysis of outcomes after extended hepatectomy. In patients with an otherwise normal liver, PVE is indicated when the standardized FLR volume is $\leq$ 20%. This cut-off point was determined by analysis of complications in 42 patients with normal underlying liver who underwent extended right hepatectomy.[51] The complication rate was increased, and intensive care unit stay and hospital stay were prolonged in patients with an FLR volume $\leq$ 20% compared with those with an FLR volume $>$ 20%. No patient died in the series. Analysis of the distribution of segmental volume variations in patients with normal liver underscores the need for systematic volumetry before extended hepatectomy: the left lateral bisegment (II and III) contributes $\leq$ 20% of TLV in $>$ 75% of patients in the absence of compensatory hypertrophy.[52]

Among patients who receive extensive chemotherapy prior to hepatic resection, liver injury can occur.[35,53,54] Although the clinical significance of chemotherapy-related liver injury is not well defined, it has been proposed that in patients who have received preoperative systemic chemotherapy, PVE is indicated when the FLR volume is $\leq$ 30% of TLV.[13,55] In patients with hepatic fibrosis/cirrhosis, data suggest that PVE is indicated when the FLR is $\leq$ 40% of TLV.[56–58]

Contraindications to PVE include FLR volume larger than the cut-off volumes specified above and tumor invasion of the portal vein to be resected because in such cases, portal flow is already diverted. Relative contraindications to PVE include tumor extension to the FLR, uncorrectable coagulopathy, biliary dilatation in the FLR (if the biliary tree is obstructed, drainage is recommended), portal hypertension, and renal failure.

Technical Details of PVE

The optimal extent of PVE before extended right hepatectomy is debated. Some propose embolization of the right portal vein only, leaving the portal veins supplying segment IV patent even if there is tumor involvement of this segment.[58–60] While PVE before extended right hepatectomy results in the desired hypertrophy of the FLR, it also increases the volume of segment IV; full diversion of portal flow to segments II and III $\pm$ I ensures the maximal stimulus for hypertrophy of the true FLR.[61,62] Segment IV hypertrophy is not desired for extended right hepatectomy because hypertrophy increases the parenchymal transection surface across this segment. A modified PVE technique in which embolization is extended to segment IV prior to extended right hepatectomy using small particles and coils has been shown to be safe and also to result in the best hypertrophy rate (69% FLR volume increase), increasing resection rates (86%) compared with other techniques.[63,64]

Incomplete embolization of tumor-bearing liver may have oncologic consequences. Although tumor growth in the nonembolized liver has been noted after right PVE, tumor size changes before and after PVE have not been reported, so the effects of PVE on tumor growth rate are not known.[65,66] Analysis of patients with disease deemed unresectable despite PVE showed that after embolization of the entire tumor-

bearing liver, changes in tumor size did not affect resectability.[67] Chemotherapy administration after PVE and before resection does not appear to retard hepatic regeneration. Thus, the technical aspects of PVE[64,68,69] are of great importance to maximize hypertrophy and to minimize the risk of tumor growth in the interval between PVE and hepatic resection.[63,64]

Outcomes from PVE Studies to Date

Systematic use of standardized FLR volumetry and PVE according to the guidelines above was validated in a large series (127 consecutive extended hepatectomies).[50] In this series, 31 patients (24%) underwent PVE prior to resection; postoperative liver insufficiency occurred in six patients (5%) and was transient in all of them. The postoperative complication rate was 31%, and only one postoperative death occurred (0.8%).

Others have confirmed that FLR volume predicts postoperative liver function and the post-hepatectomy clinical course. In a retrospective analysis of outcome following resection of colorectal liver metastases, Shoup et al.[70] found that FLR volume ≤ 25% was an independent predictor of complications and prolonged hospital stay. Elias et al.[36] demonstrated that patients considered to have unresectable tumors because of inadequate FLR volume at presentation could undergo complete resection after PVE, with a 5-year overall survival rate of 29%. Azoulay et al.[55] showed that the 5-year overall survival rate after resection in patients with colorectal liver metastases who required PVE (40%) was similar to that in patients who did not require PVE (38%).

Consensus Statement

1. Volumetry to evaluate the FLR volume is indicated if major hepatic resection (resection involving more than four segments) is planned or if the patient has underlying liver disease.
2. Preoperative PVE may be indicated when the standardized FLR volume is ≤ 20% of TLV in patients with normal liver; ≤ 30% of TLV in patients who have received extensive chemotherapy; and ≤ 40% of TLV in patients with hepatic fibrosis or cirrhosis.
3. Imaging is indicated 3–4 weeks after PVE to reassess liver volume and hypertrophy.
4. The benefits of PVE are clearly established prior to major hepatectomy in selected subsets of patients with and without chronic liver disease. There is no role for a new randomized trial of PVE.

RFA OF HEPATIC COLORECTAL METASTASES

As stated previously, hepatic resection is the only curative option for patients with hepatic colorectal metastases. Unfortunately, many hepatic tumors are considered unresectable because they are multiple or inaccessible.[71] Options for patients with unresectable disease include systemic therapy, local ablative techniques (percutaneous ethanol injection, microwave tumor coagulation, interstitial laser photocoagulation, cryosurgical ablation, or RFA), and hepatic-directed therapy (hepatic artery ligation, chemoembolization, and hepatic artery infusion).

Over the past decade, the generation of heat within a lesion by a radiofrequency current has become the preferred method of local ablation because it can effectively destroy tumors with few complications.[72–75] In 1996, the U.S. Food and Drug Administration (FDA) approved RFA for generic tissue ablation; in 2000, RFA was approved for ablation of unresectable hepatic colorectal metastases.

RFA can be performed in the operating room via celiotomy or laparoscopy or in the radiology suite by using a percutaneous approach. RFA can be performed with other modes of liver-directed therapy, such as resection and hepatic artery perfusion, and it can be used in conjunction with systemic therapy. RFA is associated with low morbidity, and retreatment for persistent or recurrent disease is feasible.[75] RFA continues to evolve; new technology has increased the potential field of ablation and simplified the technique. More recently, microwave ablation has been introduced as a rapid method of delivering high temperatures to a large area of the liver, possibly reducing local recurrence rates.

Indications

RFA has mainly been used for unresectable hepatocellular carcinoma or unresectable metastatic disease confined to the liver. Because tumors may be deemed unresectable on the basis of size, number, location, or doubling time, the preoperative work-up must include imaging to look for other sites of disease, document response to prior therapies, and

determine the nature of the disease. Some patients have resectable disease but limited hepatic reserve; for example, a patient with hepatic recurrence after previous hepatectomy may not have sufficient hepatic reserve to permit additional resection. In patients with bilobar disease, resection of larger lesions and RFA of smaller lesions may completely eradicate the tumor while preserving hepatic reserve. Finally, in patients who have multiple comorbid factors and are at high risk for complications of general anesthesia, a less invasive approach such as percutaneous RFA may be preferable to hepatic resection.

Local Recurrence and Survival Rates after RFA

Local recurrence rates after RFA are difficult to interpret across studies. Some authors report recurrences after complete ablation verified by early postoperative images obtained with CT or magnetic resonance imaging (MRI) whereas others do not confirm complete response by postoperative imaging and report recurrences based on follow-up imaging. Some investigators also report rates of recurrence within the whole liver rather than only at the site of ablation. The length of follow-up also affects recurrence rate.

Bowles et al.[72] evaluated 76 patients undergoing RFA of 328 tumors. Sixteen patients underwent repeated ablation for recurrences or new lesions. There were 30 recurrences at the site of a prior ablation. Patients with large tumors, tumor vascular invasion, and hepatic dysfunction had a significantly higher recurrence rate. Solbiati et al.[75] evaluated 117 patients undergoing percutaneous RFA of hepatic colorectal metastases and found that time to local recurrence and frequency of recurrence were influenced by lesion size. Similarly, others found that tumor size significantly influenced local recurrence of metastatic disease, independent of RFA technique.[73,74] No study has shown that differences in technique influence the rate of recurrence after a complete response.

There are very few reports of survival rates following RFA. Studies that report survival data differ in patient selection criteria, follow-up time, tumor type, and RFA approach, which make them difficult to compare. The 3-year survival rate following RFA for hepatic colorectal metastases was 37% in a study by Abdalla et al.[10] and 46% in a study by Solbiati et al.[75] In both studies, > 50% of patients had only one tumor ablated. Solbiati et al.[75] ablated liver lesions in 13 patients who had extrahepatic metastases whereas Abdalla et al.[10] ablated liver lesions in patients with localized hepatic disease only. These two studies also differed in the method of RFA: Solbiati et al.[75] used a percutaneous approach whereas Abdalla et al.[10] performed RFA via an open approach. Some patients in the Solbiati study also underwent placement of a hepatic arterial infusion pump, which may explain the slightly better outcome.

RFA versus Hepatic Resection

There is no prospective randomized controlled trial of RFA versus resection for the treatment of primary liver carcinoma or hepatic metastases. One retrospective study of 358 patients with colorectal liver metastases compared resection, RFA plus resection, RFA alone, and laparotomy with biopsy.[10] RFA was used for cure when complete resection was not possible. All patient-related and tumor-related factors known to influence outcome were similar among the groups although in a non-randomized study, selection bias cannot be ruled out, favoring RFA. The rate of recurrence was 84% after RFA alone, 63% after RFA plus resection, and 52% after resection alone. Local recurrence (in the area treated) was more common after RFA plus resection (9%) than after RFA alone (5%) or resection alone (2%). The 3-year overall survival rate was 73% after resection, 43% after RFA plus resection, and 37% after RFA alone. Patients who underwent RFA had a survival advantage over patients who underwent biopsy with or without chemotherapy.

Resection remains the first choice for patients with disease confined to the liver, in part because recent data demonstrate higher local recurrence rates after RFA than after resection. However, RFA holds promise for improving the treatment of hepatic malignancies. It is a useful adjunct to resection, and it may be a successful alternative to resection when extensive disease and limited hepatic reserve, bilobar disease, or medical conditions would preclude laparotomy. The survival advantage of RFA may be decreasing as outcome with chemotherapy improves—the median survival in patients with advanced metastatic disease treated with chemotherapy is currently reported to be >20 months. The potential advantage of adding RFA to chemotherapy is being evaluated in a randomized phase III study of RFA combined with chemotherapy versus chemotherapy alone [the Chemotherapy + LOCal ablation versus Chemotherapy (CLOCC) trial, European Organization for Research and Treatment of Cancer (EORTC) trial 40004]. Outcome data from this trial and large multicenter trials comparing RFA and

resection will help establish a comprehensive algorithm for multimodal management of patients with hepatic colorectal metastases.

Consensus Statement

1. Resection, not RFA, is the treatment of choice for patients with resectable hepatic malignancies.
2. RFA is a local therapy option in selected patients who are not candidates for resection.
3. Recurrence rates after RFA are higher than those after resection; survival rates after RFA are lower than those after resection.
4. Patients with tumors larger than 3 cm have high local recurrence rates after RFA and are not optimal candidates for this procedure.
5. Open or laparoscopic RFA is preferable because of superior probe placement with intraoperative ultrasound and the ability to detect other tumors.
6. All patients considered for RFA of hepatic colorectal metastases should be evaluated by a multidisciplinary team including a surgeon with hepatobiliary expertise.

RESECTION OF EXTRAHEPATIC DISEASE AND HILAR LYMPH NODE METASTASES

One of the main clinicopathologic characteristics of colorectal liver metastases is their tendency to spread to regional lymph nodes and contiguous or distant organs. Currently, liver resection constitutes the gold-standard treatment in patients presenting with resectable hepatic colorectal metastases provided that a complete macroscopic resection can be achieved. In the early 1990s, the best candidates for liver resection were patients with fewer than four liver metastases, each nodule < 5 cm in diameter, and onset of metastasis > 12 months after colorectal primary tumor resection. While extrahepatic disease was once considered an absolute contraindication for liver resection, today, selected patients with extrahepatic disease may be offered curative resection.

In selected patients with hepatic colorectal metastases associated with limited resectable extrahepatic disease (either hilar pedicle lymph node involvement or resectable peritoneal carcinomatosis), an aggressive surgical resection can offer hope for long-term survival. However, in such patients, surgery represents cytoreductive therapy, and a complete cure can only be obtained by means of a multidisciplinary approach including chemotherapy (systemic and in selected cases intraperitoneal).

Extrahepatic disease can be either extra-abdominal or intra-abdominal. The most common forms of intra-abdominal extrahepatic disease are hepatic pedicle lymph node metastases and peritoneal carcinomatosis.

Hepatic Pedicle Lymph Node Involvement

The incidence of hepatic pedicle lymph node metastases ranges from 3% to 33% in patients with hepatic colorectal metastases. In patients with hepatic pedicle lymph node involvement, the reported 5-year survival rate after resection of colorectal liver metastases ranges from 5% to 42%.[76,77] A prospective study evaluated whether hepatic pedicle lymph node dissection could improve the outcome in such patients.[76] This study found that the survival rate was significantly lower among patients with than among those without hepatic pedicle lymph node metastases. However, the survival rate after hepatic pedicle lymph node dissection was significantly higher among patients with node involvement limited to area 1 (hepatoduodenal ligament and retropancreatic nodes) than among patients with involvement of area 2 (common hepatic artery and celiac axis nodes). Finally, the study found that hepatic pedicle lymph node involvement was significantly more frequent in patients with more than three metastases, when the metastasis was located in segments IV and V, with a solitary resectable peritoneal deposit, or with poorly differentiated adenocarcinoma. The best strategy for patients presenting with hepatic colorectal metastases and hepatic pedicle lymph node involvement is not well defined, and the role of aggressive treatment of hepatic pedicle lymph node involvement, even when a curative resection can be achieved, is still a matter of discussion.

Peritoneal Carcinomatosis

In a large series of patients, investigators from the Gustave Roussy Institute[78,79] evaluated whether resection of extrahepatic disease could improve the outcome of patients with resectable hepatic colorectal metastases. They showed that the survival rate was significantly lower for patients with extrahepatic disease than for those without extrahepatic disease. However, they also showed that a 5-year survival rate ranging from 12% to 37% could be obtained in selected patients with extrahepatic disease depending on the type of disease (lung metastasis, primary colorectal recurrence, retroperitoneal or hepatic pedicle lymph node involvement, peritoneal carcino-

matosis, or miscellaneous). Interestingly, among patients presenting with extrahepatic disease, the survival rate was significantly higher in patients with fewer than five liver metastases, in patients who received neoadjuvant chemotherapy, and in those in whom a complete resection could be achieved. Therefore, resection of intra-abdominal extrahepatic disease during hepatectomy for colorectal liver metastases should be performed provided a negative resection margin is achieved.

Consensus Statement

1. Extrahepatic disease (except the primary colorectal tumor) is typically a contraindication to resection.
2. The rationale for resection of resectable extrahepatic disease associated with hepatic colorectal metastases has been based on the lack of nonsurgical curative therapies.
3. The incidence of hepatic pedicle lymph node involvement in patients with hepatic metastases is 3%–33% and correlates with the extent of liver disease.
4. No data convincingly demonstrate that resection of portal nodes confers a survival advantage. The presence of positive nodes in the paraaortic or celiac zone is associated with an extremely poor prognosis.
5. Extrahepatic disease in the lung that is resectable with a complete resection and local recurrence in the bowel should be resected in patients undergoing hepatic resection.
6. Resection of low-volume peritoneal carcinomatosis has not been demonstrated to improve survival and should only be performed in the context of a clinical trial.

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